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Clinical characteristics and outcomes in children hospitalised with pandemic influenza A/H1N1/09 virus infection – a nationwide survey by the Pediatric Infectious Diseases Group of Switzerland

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Abstract: **OBJECTIVE:** To describe all patients admitted to children's hospitals in Switzerland with a diagnosis of influenza A/H1N1/09 virus infection during the 2009 influenza pandemic, and to analyse their characteristics, predictors of complications, and outcome. **METHODS:** All patients 18-years-old hospitalised in eleven children's hospitals in Switzerland between June 2009 and January 2010 with a positive influenza A/H1N1/09 reverse transcriptase polymerase chain reaction (RT-PCR) from a nasopharyngeal specimen were included. **RESULTS:** There were 326 PCR-confirmed patients of whom 189 (58%) were younger than 5 years of age, and 126 (38.7%) had one or more pre-existing medical condition. Fever (median 39.1 °C) was the most common sign (85.6% of all patients), while feeding problems ($p = 0.003$) and febrile seizures ($p = 0.016$) were significantly more frequent in children under 5 years. In 142 (43.6%) patients there was clinical suspicion of a concomitant bacterial infection, which was confirmed in 36 patients (11%). However, severe bacterial infection was observed in 4% of patients. One third ($n = 108$, 33.1%) of the patients were treated with oseltamivir, 64 (59.3%, or 20% overall) within 48 hours of onset of symptoms. Almost half of the patients (45.1%) received antibiotics for a median of 7 days. Twenty patients (6.1%) required intensive care, mostly for complicated pneumonia (50%) without an underlying medical condition. The median duration of hospitalisation was 2 days (range 0-39) for 304 patients. Two children (<15 months of age with underlying disease) died. **CONCLUSIONS:** Although pandemic influenza A/H1N1/09 virus infection in children is mostly mild, it can be severe, regardless of past history or underlying disease.

DOI: <https://doi.org/10.4414/smwm.2015.14171>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-117705>

Journal Article

Published Version



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Originally published at:

Hagerman, Andres; Posfay-Barbe, Klara M; Duppenhaler, Andrea; Heininger, Ulrich; Berger, Christoph (2015). Clinical characteristics and outcomes in children hospitalised with pandemic influenza A/H1N1/09

virus infection – a nationwide survey by the Pediatric Infectious Diseases Group of Switzerland. Swiss Medical Weekly, 145:w14171.
DOI: <https://doi.org/10.4414/smw.2015.14171>

Clinical characteristics and outcomes in children hospitalised with pandemic influenza A/H1N1/09 virus infection – a nationwide survey by the Pediatric Infectious Diseases Group of Switzerland

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Summary

OBJECTIVE: To describe all patients admitted to children's hospitals in Switzerland with a diagnosis of influenza A/H1N1/09 virus infection during the 2009 influenza pandemic, and to analyse their characteristics, predictors of complications, and outcome.

METHODS: All patients ≤18-years-old hospitalised in eleven children's hospitals in Switzerland between June 2009 and January 2010 with a positive influenza A/H1N1/09 reverse transcriptase polymerase chain reaction (RT-PCR) from a nasopharyngeal specimen were included.

RESULTS: There were 326 PCR-confirmed patients of whom 189 (58%) were younger than 5 years of age, and 126 (38.7%) had one or more pre-existing medical condition. Fever (median 39.1 °C) was the most common sign (85.6% of all patients), while feeding problems ($p = 0.003$) and febrile seizures ($p = 0.016$) were significantly more frequent in children under 5 years. In 142 (43.6%) patients there was clinical suspicion of a concomitant bacterial infection, which was confirmed in 36 patients (11%). However, severe bacterial infection was observed in 4% of patients. One third ($n = 108$, 33.1%) of the patients were treated with oseltamivir, 64 (59.3%, or 20% overall) within 48 hours of onset of symptoms. Almost half of the patients (45.1%) received antibiotics for a median of 7 days. Twenty patients (6.1%) required intensive care, mostly for complicated pneumonia (50%) without an underlying medical condition. The median duration of hospitalisation was

2 days (range 0–39) for 304 patients. Two children (<15 months of age with underlying disease) died.

CONCLUSIONS: Although pandemic influenza A/H1N1/09 virus infection in children is mostly mild, it can be severe, regardless of past history or underlying disease.

Key words: H1N1/09; influenza virus; children; epidemiology; risk factors; symptoms; hospitalisation; treatment

Introduction

The pandemic influenza A/H1N1/09 virus (PIA) spread in the Swiss paediatric population after the first case was diagnosed on April 24, 2009 [1]. However, it was not until October 2009 that the number of cases and hospitalisation rates secondary to PIA infection increased notably, reaching a peak in week 49 [1]. In Switzerland, according to nationally reported data, 5–14-year-old children were the age group most frequently affected, with 438 cases of confirmed PIA infection per 100,000 inhabitants, followed by 0–4-year-old children with 364 cases per 100,000 inhabitants [1]. Similarly, in other countries the incidence of PIA was also highest in children younger than 14 years [2–4]. This study reviewed all paediatric patients hospitalised in children's hospitals in Switzerland with a diagnosis of influenza A/H1N1/09 virus infection during the 2009 influenza pandemic and analyses their characteristics, risk factors for admission to a paediatric intensive care unit (PICU), and outcomes.

Methods

In 2009, Switzerland had an estimated paediatric population (≤ 18 years of age) of 1,542,271 [5]. All children living in Switzerland have medical insurance and access to healthcare. This study was carried out in all 11 children's hospitals in the country (comprising the five university children's hospitals in Basel, Bern, Geneva, Lausanne and Zürich, and the children's hospitals of Aarau, Luzern, St. Gallen, Hôpitaux du Valais, Fribourg and Triemli in Zurich, all but the latter three having a paediatric intensive care unit supplying mechanical ventilation) between June 2009 and January 2010. All patients ≤ 18 years old, hospitalised with a positive influenza A/H1N1/09 virus quantitative reverse transcriptase polymerase chain reaction (RT-PCR) from a nasopharyngeal specimen (swab or aspirate), were included. Demographic and clinical characteristics, laboratory and radiological data, treatment, hospital evolution and outcome were obtained prospectively or retrospectively immediately after the pandemic from medical charts by use of a uniform, standardised case-report form.

Influenza A/H1N1/09 virus was first detected in April 2009 in Switzerland. The outbreak, however, started on week 44 of 2009 and lasted until week 2 of 2010.

This study was conducted in accordance with the principles and standards of Good Clinical Practice, with the Helsinki Declaration, and with the ethics boards' approval.

Statistical analyses were carried out using SPSS (PASW Statistics 18.0.0; IBM Corporation, Somers, NY). Standard descriptive statistics were used to describe demographics, outcomes and clinical characteristics. Categorical data

were compared with chi-square tests, or Fisher's exact test when appropriate. Characteristics of children were compared by using Student's t-test, linear regression or Mann-Whitney-U/Kruskal-Wallis tests, according to the type of independent variable. Multivariate analysis was used to determine predictors of PICU admission. For all statistical tests, differences were considered significant when p-values were < 0.05 .

Results

Three hundred and twenty six PCR-confirmed PIA-positive children were hospitalised between June 2009 and January 2010 (median age at admission 43.7 months, (range 0 to 219.7) in all eleven children's hospitals in Switzerland. Rapid antigen tests for influenza were performed at the time in 42 patients (12.9%). Among these, 28 patients (66.7%) had a positive test result. Seventy-three infants (22%) were < 1 year-old and 190 (58.3%) were male. The peak (87.1%) of PIA-related hospitalisations occurred between November and December 2009. One hundred and twenty-six children (38.7%) had one or more pre-existing medical condition (table 1), neurological disease and prematurity (defined as birth at less than 37 weeks gestational age) being the most frequent conditions.

Vaccination against influenza

Twenty-one children (6.4%) were vaccinated against PIA before admission, most of them (95%) because of a known chronic disease, following national recommendations [6].

Table 1: Underlying medical conditions in 126 of 326 Swiss children hospitalised with pandemic influenza A/H1N1/09 virus infection. (> 1 condition reported in some children.)

Pre-existing condition	n (%)	Vaccinated children n (%)
Neurological disease *	27 (18.1)	3 (14)
Prematurity	20 (13.4)	
Asthma / recurrent wheezing	18 (12.1)	1 (5)
Genetic disease [†]	10 (6.7)	1 (5)
Cancer [¶]	9 (6)	3 (14)
Chronic lung disease [§]	7 (4.7)	4 (19)
Cardiovascular disease [‡]	6 (4)	2 (10)
Inborn errors of metabolism ^{**}	6 (4)	1 (5)
Sickle cell disease	5 (3.4)	1 (5)
Renal disease ^{††}	5 (3.4)	
Diabetes mellitus	4 (2.7)	
Haematological disease ^{¶¶}	4 (2.7)	1 (5)
Immunodeficiency ^{§§}	4 (2.7)	1 (5)
Crohn's disease	2 (1.3)	
Other ^{‡‡}	22 (14.8)	2 (10)
No comorbidities		1 (5)
Total	149 (100)	21 (100)

* Seizures/epilepsy n = 9; recurrent febrile seizures n = 3.

† Down's syndrome n = 2.

¶ Leukaemia n = 5.

§ Cystic fibrosis n = 4.

‡ Primary pulmonary hypertension n = 2, heart transplantation n = 1.

** Mitochondrial disorder, citrullinaemia, tyrosinaemia, leucinoses.

†† Renal transplantation n = 1.

¶¶ Bone marrow transplantation (other than cancer) n = 2.

§§ Asplenia, mannose binding lectin deficiency, hypogammaglobulinaemia, congenital human immunodeficiency virus infection.

‡‡ Stevens-Johnson syndrome, Kawasaki disease, Addison's disease, chronic recurrent multifocal osteomyelitis, severe burns, portal vein thrombosis, transitory synovitis of the hip.

Only two patients were vaccinated twice. Eighteen patients were vaccinated 1–54 days (median 7, interquartile range [IQR] 12) before onset of disease; two patients were vaccinated 3 and 4 days after the onset of symptoms (missing data for one patient).

Hospital admission

Hospital admission was at a median of 2 days (range 0–39, IQR 4) after the beginning of illness in 308 patients (15 patients were already hospitalised, missing data for 3 patients). Reasons for hospital admission are summarised in table 2: >80% of children were admitted with a respiratory tract infection, febrile seizures, or vomiting/dehydration. In the initial stages of illness, respiratory symptoms alone appeared a median of 4 days (range 0–25, IQR 4) before admission in 170 patients.

Admission to intensive care unit

Twenty (6.1%) of 326 patients were admitted to the PICU. Of these, six (30%) were 0–4 years of age including three <12 months; eight (40%) were 5–11 years old and six (30%) were 12–18 years old. Older children (12–18 years old) had proportionately a higher likelihood to be admitted to the PICU than the younger age groups (12.2% vs 0–4 [3.2%] and 5–11 years old [9.1%], $p = 0.025$), but they also had more comorbidities (61.2% vs 42.2% and 21.3%, respectively, $p < 0.001$). The main reason for PICU admission was complicated pneumonia ($n = 10$, 50%). Six (30%) patients required mechanical ventilation. The median stay in the PICU was 3 days (range 1–21, IQR 4). In the multivariate analysis, only older age group was a predictor of PICU admission.

Hospital stay and death

The median duration of hospitalisation was 2 days (range 0–36, IQR 3) for 304 patients (excluding 15 patients with nosocomial influenza), and data were missing for seven foreign patients who were transferred back to hospitals in their home countries.

Among the 326 hospitalised children, two (0.6%) died which results in a mortality of 0.13 per 100,000 children. One was a 5-month-old boy with an unknown syndrome who died after a cardiac arrest and was declared dead on arrival in the hospital. On autopsy, bacterial pneumonia was found as cause of death. The second patient was a 15-month-old girl with a history of pre-B acute lymphoblastic leukaemia. She was admitted because of febrile neutropenia and pneumonia on the day of onset of symptoms, and died from cardiorespiratory failure 8 days later.

Clinical presentation

Signs and symptoms during hospital stay are described in table 3. Fever was the most common sign (median 39.1 °C, IQR 0.8), present in 85.6% of all patients. Feeding problems, febrile seizures, and conjunctivitis were significantly more frequent in children <5 years old compared with older age groups.

Chest radiography was performed in 136 patients, and was normal in 25 children (18.4%). The remaining 111 patients had one or more of the following abnormal findings: peribronchial or perihilar ($n = 51$; 37.5%), lobar ($n = 48$; 35.3%), or multilobar ($n = 21$; 15.4%) infiltrates, pleural effusion ($n = 16$; 11.8%), atelectasis ($n = 15$; 11%), and interstitial infiltrates ($n = 14$; 10.3%). Thus, 85 of 136 patients (62.5%) had radiological signs of pneumonia. Oxygen supplementation was required in 79 patients (24.2%), mostly in patients <5 years old (48/79; 60.8%), a third being less than 12 months of age (18 of 48; 37.5%).

Among all hospitalised patients, 142 (43.6%) had suspected bacterial infection (based on clinical, biological, or radiological evaluation by the physician in charge and prompting antibiotic treatment), including severe bacterial infections, such as sepsis or septic shock ($n = 7$), toxic shock syndrome ($n = 3$), meningitis ($n = 1$), mastoiditis ($n = 1$), or bacterial peritonitis ($n = 1$). Pneumonia on chest radiography was diagnosed in 85 patients: four children developed pleural effusion and one had empyema. Three children had a complicated necrotising pneumonia secondary

Table 2: Reasons for hospitalisation of 326 children with laboratory-proven pandemic influenza A/H1N1/09 virus (PIA) infection.

Admission diagnosis	n (%)
Related to PIA infection	279 (85.6)
Respiratory tract infection	163 (61.1)
Bronchiolitis	12 (3.7)
Febrile seizure	35 (13.1)
Gastroenteritis/vomiting/dehydration	19 (7.1)
Nonfebrile seizures / epilepsy	12 (4.5)
Severe influenza-like illness	10 (3.8)
Associated bacterial infection	12 (3.7)
Neurological problem*	8 (3)
Feeding problem	7 (2.6)
Social problem	5 (1.9)
Neutropenia	3 (1.1)
Vaso-occlusive crisis (sickle cell)	2 (0.7)
Other	3 (1.1)
Associated with PIA infection	47 (14.4)
Nosocomial PIA infection	15 (4.6)
Risk for complications secondary to PIA infection due to underlying disease	10 (3.1)
Others†	22 (6.7)

* Encephalitis, meningitis signs, facial palsy.

† Surgical procedures, trauma, idiopathic thrombocytopenic purpura, Stevens-Johnson syndrome, diabetic ketoacidosis, inborn errors of metabolism.

to *Staphylococcus aureus* (n = 1) or *Streptococcus pneumoniae* (n = 2) infection. Four patients had a clinical diagnosis of atypical pneumonia. Secondary bacterial infection was microbiologically proven in 36 (25.4%) of 142 patients with suspected bacterial infection, which corresponds to 11% of all patients hospitalised with PIA infection. The most frequently isolated bacteria were *S. pneumoniae* (n = 10) and *S. aureus* (n = 5). Children with secondary bacterial infection were significantly older than those without (86 vs 61 months, p = 0.018), but gender distribution was not different between groups.

Treatment

Antibiotics were prescribed in 147 patients (45.1%), most commonly amoxicillin with clavulanic acid (n = 61), amoxicillin (n = 24), and ceftriaxone (n = 21). Combination antimicrobial therapy was used in 14 patients, usually comprising a third generation cephalosporin with an aminoglycoside (n = 7). The main reason for antibiotic use was a respiratory tract infection, in particular suspected bacterial pneumonia. In three patients, antibiotics were reported as prescribed prophylactically. The median duration of antibiotic treatment was 7 days (range 1–35, IQR 5).

Oseltamivir was prescribed in 108 patients (33.1%), for a median duration of 5 days (range 2–10, IQR 0). In 64 (59.3%) of these patients oseltamivir was administered within 48 hours of onset of symptoms. Median duration of hospitalisation in these 64 children was 2.5 days (range 1–63, IQR 3), while it was 2 days for the children receiving oseltamivir after 48 hours (p = 0.064). Median duration of hospitalisation for children not treated with oseltamivir was 3.4 days (range 0–32). Among 64 oseltamivir-treated patients before 48 hours, 32 (50%) were <5 years of age and 39 (60.9%) patients had a pre-existing medical condition. Pneumonia was observed in 7 (10.9%) of 64 patients treated with oseltamivir within 48 hours, and in 78 (29.8%)

of 262 not treated with oseltamivir or treated >48 hours after onset of disease (p <0.001). Four (6.2%) of 64 children treated with oseltamivir within 48 hours were admitted to the paediatric intensive care unit (PICU), where two of them required mechanical ventilation. The use of oseltamivir did not decrease the risk of admission to the PICU (odds ratio 1.025; 95% confidence interval 0.331 to 3.178).

Discussion

This study describes all children admitted to paediatric hospitals in Switzerland with confirmed influenza A/H1N1/09 disease during the 2009 influenza pandemic. Most of the children were less than 5 years old and a significant proportion of patients were younger than 1 year of age, both findings being similar to the previous influenza season (2008/2009) in Switzerland [7]. According to the national database, the hospitalisation rate for pandemic influenza in Switzerland was 72 per 1,000 confirmed cases in the 0–4 years age group or 26 per 100,000 children 0–4 years of age, which was the highest after the >65 years-old group [1].

In our study, the calculated incidence was almost twice as much, i.e. 49/100,000 (189 of 382,170 children 0–4 years of age living in Switzerland at the end of the year 2009; <http://www.bfs.admin.ch/bfs/portal/de/index/themen/01.html>). This discrepancy indicates that underreporting of cases through the national pandemic influenza surveillance system had occurred.

Time between onset of disease and hospital admission was unusually short. This may be related to the virulence of this particular pandemic influenza virus and/or increased media attention that might have caused fear, not only amongst parents but also amongst healthcare workers leading to rapid hospitalisations.

Table 3: Signs and symptoms before or during hospital stay in 326 children with laboratory-proven influenza A/H1N1/09 virus infection, by age group.

	Age group in years (%) [*]			p-value	Total (%) [†]
	0–4 189 58%	5–11 88 27%	12–18 49 15%		326
	n (%)	n (%)	n (%)	n (%)	n (%)
Fever ≥38 °C	163 (86.2)	75 (85.2)	41 (85.4)	NS	279 (85.6)
Cough	154 (81.5)	71 (80.7)	39 (79.6)	NS	264 (81)
Rhinitis	149 (78.8)	57 (64.7)	32 (65.3)	NS	238 (73)
Pharyngitis	60 (31.7)	40 (45.5)	19 (38.8)	NS	119 (36.5)
Feeding problems	82 (43.4)	20 (22.7)	13 (26.5)	0.003	115 (35.3)
Vomiting	53 (28.0)	25 (28.4)	15 (30.6)	NS	93 (28.5)
Dyspnoea	50 (26.5)	25 (28.4)	16 (32.7)	NS	91 (27.9)
Wheezing	45 (23.8)	25 (28.4)	11 (22.4)	NS	81 (24.8)
Diarrhoea	44 (23.3)	13 (14.7)	5 (10.2)	NS	62 (19)
Conjunctivitis	16 (8.4.7)	11 (12.5)	0 (0)	0.022	27 (8.3)
Exanthema	7 (3.7)	8 (9.1)	5 (10.2)	NS	20 (6.1)
Hoarseness	9 (4.8)	7 (8.0)	1 (2.0)	NS	17 (5.2)
Croup-like coughing	8 (4.2)	5 (5.7)	2 (4.1)	NS	15 (4.6)
Pneumonia	43 (22.8)	29 (33.0)	12 (24.5)	NS	84 (25.8)
Febrile seizures	35 (18.5)	11 (12.5)	1 (2.0)	0.016	47 (14.4)
Otitis media	22 (11.6)	4 (4.5)	1 (2.0)	NS	27 (8.3)
Bronchiolitis	10 (5.3)	1 (1.1)	1 (1.7)	NS	12 (3.7)

^{*} Within sign or symptom.

[†] Within total of patients.

Approximately one-third of hospitalised children in our study had an underlying medical condition. This is comparable to other paediatric studies, which reported an underlying condition as a risk factor for hospital admission in 32% to 75% of patients during the same pandemic [8–14]. As in other studies, the main cause for hospitalisation was respiratory tract disease, followed by gastrointestinal symptoms in all age groups [9, 10, 12]. Asthma was identified by others as a major risk factor for admission in the PICU [8]. In our study, only 12% of hospitalised children had asthma and only one patient was admitted to the PICU.

Influenza is known to cause febrile seizures in children [15]. Most of the patients admitted with febrile seizures in our study did not have a prior history of neurological disease. However, the true incidence of febrile seizures in children with pandemic influenza A/H1N1/09 virus infection is difficult to assess, because children with uncomplicated febrile seizures are often not admitted to hospital [16]. We observed an unusually high proportion of severe bacterial co-infections, which does not concur with other paediatric reports describing much lower rates (<5%) [8, 12, 17]. This could be explained by the fact that bacterial co-infection was actively searched for in most patients, because of the notion that influenza-associated paediatric mortality is usually linked with bacterial co-infection [18, 19]. As a consequence, almost 50% of our patients were initially treated with antibiotics. The design of this study prevents us from establishing if this high use of antibiotics had an impact on disease outcome. However, the paediatric mortality rate secondary to PIA infection during the 2009 influenza pandemic in Switzerland was low and the two fatalities that occurred were in children with severe underlying medical conditions. The relatively small number of patients admitted to PICU is probably explained by the fact that the pandemic overall was less severe than anticipated and access to healthcare is easy in Switzerland, leading to rapid interventions. In our study, only older age (12–18 years old) was a predictor of PICU admission. However, it should be noted that comorbidity was also significantly higher in children hospitalised in this age group. Interestingly, children admitted to PICU with complicated pneumonia had no pre-existing conditions, such as immunosuppression or chronic lung disease.

Oseltamivir was prescribed in approximately one-third of our patients and in a little more than half of the patients this was done within the recommended time frame, i.e. within 48 hours of onset of symptoms. It may seem surprising that such a low percentage of children were treated although official recommendations called for treatment of all hospitalised children. It is likely that Swiss paediatricians hesitated to treat with oseltamivir because of early reports from the southern hemisphere about the small effect of oseltamivir on symptoms and on transmission [20, 21]. Similarly, in our study oseltamivir treatment did not appear to reduce the risk of PICU admission. However, the number of patients admitted was low and this may reflect a lack of power of our study.

Vaccinating children ≥ 6 months of age against influenza and taking advantage of indirect protection of young children by vaccinating their parents and other household members could have had a significant effect in decreasing

hospitalisation rates among infants. Early in the course of the pandemic, the Swiss Federal Committee for Vaccinations had recommended that children ≥ 6 months of age with underlying disease should be vaccinated with pandemic influenza vaccine as soon as possible [6]. However, because of the belated authorisation by the Swiss regulatory agency, only a small percentage of children at risk were immunised before the pandemic reached its peak. This explains the low number of vaccinated children and the short period between vaccination and illness in several patients. Influenza vaccination rates in children in Switzerland are unfortunately unavailable for this period.

Our study has several limitations. First, it was not performed prospectively in all centres. However, all data was retrieved from the medical charts less than 6 months after hospital admission by paediatric infectious disease specialists using a standardised case-report form. Second, although the setting included all paediatric hospitals in Switzerland we cannot exclude the possibility that paediatric patients with influenza, especially adolescents, were admitted to medical centres for adults. Nevertheless, it is likely that the most severe cases and those with longer hospital stays would have been transferred to a children's hospital rapidly after admission. Finally, because the cases in the paediatric community were not reported systematically, predictors of hospitalisation could not be evaluated. However, although there were similar results to those of previous studies, confirming the clinical aspects of the disease [8–12, 17], we show that pandemic influenza A/H1N1/09 virus infection in children can be associated with increased disease severity regardless of past history or underlying disease, even in the young age group, as has been shown for seasonal influenza [22].

Disclosures: No financial support and no other potential conflict of interest relevant to this article was reported.

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